PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients: protocol for a systematic review and network meta-analysis
AUTHORS	Schwingshackl, Lukas; Chaimani, Anna; Hoffmann, Georg; Schwedhelm, Carolina; Boeing, Heiner

VERSION 1 - REVIEW

REVIEWER	IGHO ONAKPOYA UNIVERSITY OF OXFORD, UK
REVIEW RETURNED	28-Oct-2016

GENERAL COMMENTS	This protocol is a well written and structured protocol for the intended systematic review; the results of which could have implications for future dietary approaches for CVD management. A minor revisions is required to improve the quality of the research. Line 56-57: Variations in trial designs and regimen will also likely be a limitation in this review Line 151-152. Blood pressure is the most important "modifiable" risk factor. Age and family history are other very important risk factors. The authors should revise the statement (and use appropriate references). Line 158-158: So if studies do not measure blood pressure in patients who sat 3-5 minutes, will those studies be excluded? Why did the authors not consider hypertensives or pre-hypertensives with other comorbidities in their inclusion criteria? This could also influence sub-group analyses results.

REVIEWER	Yoko Yokoyama Graduate School of Media and Governance Keio University Japan
REVIEW RETURNED	20-Nov-2016

GENERAL COMMENTS	Authors describes the protocol for a systematic-review and network meta-analysis of randomized controlled trials about the impact of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients. The proposed systematic review and network meta-analysis is an important and clinically relevant topic. However, the following points need to be addressed to improve the manuscript.

1) How would you deal the data from combined dietary intervention (e.g. low-fat and low sodium)? Are you going to include it both low-fat and low sodium diet in this case? Then how would you deal those in network meta-analysis?

2) Please include search terms which would be needed to cover all dietary intervention that meet the inclusion criteria (e.g. low-sodium).

3) It seems like include dietary interventions include nutrition level (low or high carbohydrate, protein and fat) and food level (vegetarian, Mediterranean, DASH, etc).
Some food level diet intervention itself could be low-fat or low-sodium compared with control diet. How would authors plan to deal with those problems? Is it reasonable to compare those all dietary interventions in network meta-analysis?

4) Please mention ITT analysis data will be used when it is available.

5) Data extraction: Risk factors related with life style should be include (e.g. alcohol intake, smoking).

6) Study selection criteria: What is your plan when the study has shorter and longer outcomes? Would authors choose longer outcomes? Is that changed if drop-out rate is different?

7) Please describes your plan when publication bias would detect.

I look forward to reading the outcomes of this work.

REVIEWER	Dr. George Kelley West Virginia University, USA
REVIEW RETURNED	26-Nov-2016

| GENERAL COMMENTS | GENERAL COMMENTS

This protocol addresses an important topic regarding the effects of different types of diets on resting systolic and diastolic pressure in pre-hypertensive and hypertensive adults, and the use of the network meta-analytic approach is ideally suited for addressing this research question. My specific comments appear below with line and page numbers representing the actual page numbers of the manuscript itself.

SPECIFIC COMMENTS

* Page 1 (Title) - Suggest that you include the word "protocol" in the title so as to clearly distinguish it from any results-driven manuscripts that may derive from this. For example: "Impact of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients: protocol for a systematic review and network meta-analysis"

* Page 2, line 24 – Place a comma after the word "Association"

* Page 2, line 31 – I believe that "google scholar" should be "Google Scholar" |

* Page 3, line 48 – If allowed, I would suggest that you add the keywords "systematic review"

* Page 3, line 51 – Insert the word "of" after the word "question"

* Page 3, line 55 - To be consistent with the first and third bullets, remove the period after the word "synthesis"

* Page 3, line 56 and 57– Inherent to all aggregate data meta-analyses, please rewrite to include "ecological fallacy" as a potential limitation. For example: "Limitations include adherence to dietary protocols, lack of blinding across the included intervention trials and ecological fallacy"

* Page 4, line 62 – Replace "to" with "for" after the word "accounts"

* Page 4, line 67 - Place a comma after "Hypertension"

* Page 4, line 79 – Replace "up to date no" with "no up to date"

* Page 4, line 81 – Delete "i.e."

* Page 6, lines 90 and 91 – Suggest that you rewrite this sentence. How about this: "This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42016049243)."

* Page 6, line 93 – Replace "review" with "reviews"

* Page 6, line 98 – you say you're going to limit your studies to the term "Randomized (controlled) designs" which would probably lead a reader to assume that you are including indirect evidence studies only. However, as I read further in the manuscript, it appears that you will be including both direct and indirect studies, which as you know is one of the very reasons for conducting a network meta-analysis. Given the former, I would suggest that you use the term "randomized trials" versus "randomized controlled trials" here and throughout the rest of the manuscript except for those sections where you are talking about randomized controlled trials with respect to indirect evidence.

* Page 6, line 111 – Insert the word "it" after the word "since"

* Page 7, line 118 – Insert the word "the" after the word "on"

* Page 7, lines 119 through 121 – To aid the reader, here is where you might want to use the terms direct and indirect evidence as you describe what types of interventions you will include. For example: "We will include all intervention trials that meet the above inclusion criteria and include at least one of the following intervention diets and a control group (indirect evidence) or at least two intervention diets (direct evidence)"

* Page 7, line 122 – Delete ", e.g.:" and replace with "as follows:"

* Page 7, line 130 – Since this refers to a low-fat diet, I think you mean "<30% fat" versus "<30% carbohydrates"

* Page 7, line 132 – Suggest that you replace "and" with "or"

* Page 8, line 151 – Place a comma after "above"

* Page 8, line 152 – Insert "that a" after the word "show"

* Page 8, line 157 – Do you mean reference 8 or reference 9 here?

* Page 8, lines 156 to 159 – Please try to integrate this information more nicely with the information that precedes it.

* Page 8, line 164 – Delete "November 2016"

* Page 9, lines 171 and 172 – Would it not be better to redo this search string so that only the search term "random*" is used here to represent randomized trials, controlled or uncontrolled?

* Page 9, line 174 – Delete the semicolon and insert a comma after the word "articles"

* Page 9, line 185 – Suggest that you delete "(full-text)". On the same line, suggest you replace "When a study was…" with "If a study is…"

* Page 9, after line 188 – Suggest you insert the following as the first sentence: "The following data will be extracted from each study:" If you do this, on line 189 replace "First" with "first"

* Page 10, line 190 – Per my previous comments regarding direct and indirect evidence, suggest you delete the word "controlled"

* Page 10, line 200 – Suggest you replace "detected" with "assessed"

* Page 10, line 204 – Delete "E.g.," and replace with "For example,"

* Page 10, line 210 – Replace "RCTs" with "randomized trials"

* Page 10, line 212 – Insert "to" after the word "according"

* Page 11, line 218 – Suggest you replace "some important" with "selected"

* Page 11, line 221 – Suggest you insert "(circles)" after the word "nodes"

* Page 11, line 222 – Suggest your replace "lines" with "edges (lines)"

* Page 11, line 224 – Replace "in" with "on"

* Page 11, line 225 – While I'm not sure, it appears that you're using the pairs format for this meta-analysis. If so, please provide a rationale for using this approach over approaches such as the augmented and standard formats (see: White, I. R. (2015). "Network meta-analysis." Stata Journal 15(4): 951-985.)

* Page 12, lines 239 through 241 – You say that you will use ranking probabilities and surface under the cumulative ranking curves (SUCRA), which I'm fine with. However, others may argue that since treatment effects are considered as fixed parameters when a frequentist versus Bayesian approach is used, SUCRA values are

	no better than simply ranking treatments by their point estimates (see: Rucker, G. and G. Schwarzer (2015). "Ranking treatments in frequentist network meta-analysis works without resampling methods." BMC Medical Research Methodology 15: 58.) * Page 12, lines 248 through 250 – Suggest that you rewrite this sentence as follows: We plan on including changes in body weight and mean baseline age as potential effect modifiers. * Page 12, line 258 – Insert a comma after "purpose" * Page 12, line 262 – Delete the colon after "for"

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This protocol is a well written and structured protocol for the intended systematic review; the results of which could have implications for future dietary approaches for CVD management. A minor revisions is required to improve the quality of the research.

Line 56-57: Variations in trial designs and regimen will also likely be a limitation in this review
Comment: has been added

Line 151-152. Blood pressure is the most important "modifiable" risk factor. Age and family history are other very important risk factors. The authors should revise the statement (and use appropriate references).
Comment: A comment on non-modifiable risk factors has been added, together with corresponding References.

Line 158-158: So if studies do not measure blood pressure in patients who sat 3-5 minutes, will those studies be excluded?
Comment: Ideally, patients should hold a sitting position for 3-5 min prior to measurement. We are aware of the fact that this might not be explicitly stated in the study design. This will be covered by additional sensitivity analyses.

Why did the authors not consider hypertensives or pre-hypertensives with other comorbidities in their inclusion criteria? This could also influence sub-group analyses results.
Comment: has been added

Reviewer: 2

Authors describes the protocol for a systematic-review and network meta-analysis of randomized controlled trials about the impact of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients. The proposed systematic review and network meta-analysis is an important and clinically relevant topic. However, the following points need to be addressed to improve the manuscript.

1) How would you deal the data from combined dietary intervention (e.g. low-fat and low sodium)? Are you going to include it both low-fat and low sodium diet in this case? Then how would you deal those

in network meta-analysis?
Comment: If we identify a study, which combines low sodium and a low fat diet (and not fulfil the criteria of a DASH diet), we will handle this study as evaluating a different dietary regimen (low fat + low sodium) in the network MA.

2) Please include search terms which would be needed to cover all dietary intervention that meet the inclusion criteria (e.g. low-sodium).
Comment: has been added

3) It seems like include dietary interventions include nutrition level (low or high carbohydrate, protein and fat) and food level (vegetarian, Mediterranean, DASH, etc).
Some food level diet intervention itself could be low-fat or low-sodium compared with control diet. How would authors plan to deal with those problems? Is it reasonable to compare those all dietary interventions in network meta-analysis?
Comment: Thank you very much for this helpful comment. We choose these specific dietary regimens according to well established definitions, and since these belong to the most established and most known dietary patterns. Until the writing of this protocol, only preliminary searches were performed. We don't know how many dietary regimens will be available. It´s possible that following a more thorough literature search additional patterns will emerge, including food-based interventions. If food-based interventions fulfil also the criteria of a nutrient-based dietary regimen, we will perform sensitivity analysis for food-based vs. nutrient based dietary regimen taking into account possible overlaps. Moreover, we will add a Limitation section paragraph describing this problem in the final manuscript.

4) Please mention ITT analysis data will be used when it is available.
Comment: has been added

5) Data extraction: Risk factors related with life style should be include (e.g. alcohol intake, smoking).
Comment: has been added

6) Study selection criteria: What is your plan when the study has shorter and longer outcomes? Would authors choose longer outcomes? Is that changed if drop-out rate is different?
Comment: We will perform meta-regression analyses accounting for the different time points across studies.

7) Please describes your plan when publication bias would detect.
We added in the section "small study effects and publication bias" that we will fit a section model to obtain a 'adjusted' for publication bias treatment effects.

GENERAL COMMENTS

This protocol addresses an important topic regarding the effects of different types of diets on resting systolic and diastolic pressure in pre-hypertensive and hypertensive adults, and the use of the network meta-analytic approach is ideally suited for addressing this research question. My specific comments appear below with line and page numbers representing the actual page numbers of the manuscript itself.

SPECIFIC COMMENTS

* Page 1 (Title) - Suggest that you include the word "protocol" in the title so as to clearly distinguish it

from any results-driven manuscripts that may derive from this. For example: "Impact of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients: protocol for a systematic review and network meta-analysis"
Comment: has been corrected

* Page 2, line 24 – Place a comma after the word "Association"
Comment: has been corrected

* Page 2, line 31 – I believe that "google scholar" should be "Google Scholar"
Comment: has been corrected

* Page 3, line 48 – If allowed, I would suggest that you add the keywords "systematic review"
Comment: has been corrected

* Page 3, line 51 – Insert the word "of" after the word "question"
Comment: has been corrected

* Page 3, line 55 - To be consistent with the first and third bullets, remove the period after the word "synthesis"
Comment: has been corrected

* Page 3, line 56 and 57– Inherent to all aggregate data meta-analyses, please rewrite to include "ecological fallacy" as a potential limitation. For example: "Limitations include adherence to dietary protocols, lack of blinding across the included intervention trials and ecological fallacy"
Comment: has been corrected

* Page 4, line 62 – Replace "to" with "for" after the word "accounts"
Comment: has been corrected

* Page 4, line 67 - Place a comma after "Hypertension"
Comment: has been corrected

* Page 4, line 79 – Replace "up to date no" with "no up to date"
Comment: has been corrected
* Page 4, line 81 – Delete "i.e."
Comment: has been corrected

* Page 6, lines 90 and 91 – Suggest that you rewrite this sentence. How about this: "This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42016049243)."
Comment: has been corrected

* Page 6, line 93 – Replace "review" with "reviews"
Comment: has been corrected

* Page 6, line 98 – you say you're going to limit your studies to the term "Randomized (controlled) designs" which would probably lead a reader to assume that you are including indirect evidence studies only. However, as I read further in the manuscript, it appears that you will be including both direct and indirect studies, which as you know is one of the very reasons for conducting a network meta-analysis. Given the former, I would suggest that you use the term "randomized trials" versus "randomized controlled trials" here and throughout the rest of the manuscript except for those sections where you are talking about randomized controlled trials with respect to indirect evidence.

Comment: has been corrected

* Page 6, line 111 – Insert the word "it" after the word "since"
Comment: has been corrected

* Page 7, line 118 – Insert the word "the" after the word "on"
Comment: has been corrected

* Page 7, lines 119 through 121 – To aid the reader, here is where you might want to use the terms direct and indirect evidence as you describe what types of interventions you will include. For example: "We will include all intervention trials that meet the above inclusion criteria and include at least one of the following intervention diets and a control group (indirect evidence) or at least two intervention diets (direct evidence)"
Comment: has been corrected

* Page 7, line 122 – Delete ", e.g.:" and replace with "as follows:"
Comment: has been corrected

* Page 7, line 130 – Since this refers to a low-fat diet, I think you mean "<30% fat" versus "<30% carbohydrates"
Comment: has been corrected

* Page 7, line 132 – Suggest that you replace "and" with "or"
Comment: has been corrected

* Page 8, line 151 – Place a comma after "above"
Comment: has been corrected

* Page 8, line 152 – Insert "that a" after the word "show"
Comment: has been corrected

* Page 8, line 157 – Do you mean reference 8 or reference 9 here?
Comment: has been corrected

* Page 8, lines 156 to 159 – Please try to integrate this information more nicely with the information that precedes it.
Comment: has been corrected. We are aware of the fact that details of blood pressure measurements might not be explicitly stated in the respective study design. This will be covered by additional sensitivity analyses.

* Page 8, line 164 – Delete "November 2016"
Comment: has been corrected

* Page 9, lines 171 and 172 – Would it not be better to redo this search string so that only the search term "random*" is used here to represent randomized trials, controlled or uncontrolled?
Comment: has been corrected

* Page 9, line 174 – Delete the semicolon and insert a comma after the word "articles"
Comment: has been corrected

* Page 9, line 185 – Suggest that you delete "(full-text)". On the same line, suggest you replace "When a study was…" with "If a study is…"

Comment: has been corrected

* Page 9, after line 188 – Suggest you insert the following as the first sentence: "The following data will be extracted from each study:" If you do this, on line 189 replace "First" with "first"
Comment: has been corrected

* Page 10, line 190 – Per my previous comments regarding direct and indirect evidence, suggest you delete the word "controlled"
Comment: has been corrected

* Page 10, line 200 – Suggest you replace "detected" with "assessed"
Comment: has been corrected

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* Page 10, line 210 – Replace "RCTs" with "randomized trials"
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Comment: has been corrected

* Page 11, line 218 – Suggest you replace "some important" with "selected"
Comment: has been corrected

* Page 11, line 221 – Suggest you insert "(circles)" after the word "nodes"
Comment: has been corrected

* Page 11, line 222 – Suggest your replace "lines" with "edges (lines)"
Comment: has been corrected

* Page 11, line 224 – Replace "in" with "on"
Comment: has been corrected

* Page 11, line 225 – While I'm not sure, it appears that you're using the pairs format for this meta-analysis. If so, please provide a rationale for using this approach over approaches such as the augmented and standard formats (see: White, I. R. (2015). "Network meta-analysis." Stata Journal 15(4): 951-985.)

Comment: We can't see in which part of the text this was implied. The "pairs" format will be used for the direct meta-analysis and the "augmented" format for the network meta-analysis. To clarify this we added in the text: "Multi-arm trials will be modeled properly accounting for the correlation in the effect sizes from such studies".

* Page 12, lines 239 through 241 – You say that you will use ranking probabilities and surface under the cumulative ranking curves (SUCRA), which I'm fine with. However, others may argue that since treatment effects are considered as fixed parameters when a frequentist versus Bayesian approach is used, SUCRA values are no better than simply ranking treatments by their point estimates (see: Rucker, G. and G. Schwarzer (2015). "Ranking treatments in frequentist network meta-analysis works without resampling methods." BMC Medical Research Methodology 15: 58.)

Comment: We do not agree with the reviewer that "SUCRA values are no better than simply ranking

treatments by their point estimates" and this is nowhere reported in the paper by Rucker and Schwarzer.

The paper says that: "From a Bayesian perspective, parameters such as those describing the relative effectiveness of two treatments are random variables and as such have a probability distribution. Thus statements such as 'treatment A is superior to treatment B with probability 60 %' or 'Treatment A ranges under the three best of ten treatments with probability 80 %' are possible. By contrast, from a frequentist perspective, treatment effects are thought as fixed parameters and thus, strictly speaking, a concept like 'the probability that A is better than B' does not make sense."

The point the authors want to make is that when the analysis is performed in a Frequentist framework is not very intuitive to use ranking probabilities. However, in fact within Stata ranking probabilities are estimated using a Bayesian approach and therefore they take into account the uncertainty of the relative effects. The authors clarify in their paper that "we propose a frequentist analogue to SUCRA which we call P-score that works without resampling" and "we demonstrate that the numerical values of SUCRA and P-Score are nearly identical".

Consequently, we prefer to stick with the ranking probabilities and SUCRAs as this in the only available method in Stata to date, which is the software we will use for all analyses.

* Page 12, lines 248 through 250 – Suggest that you rewrite this sentence as follows: We plan on including changes in body weight and mean baseline age as potential effect modifiers.
Comment: has been corrected

* Page 12, line 258 – Insert a comma after "purpose"
Comment: has been corrected

* Page 12, line 262 – Delete the colon after "for"
Comment: has been corrected

VERSION 2 – REVIEW

REVIEWER	Igho Onakpoya University of Oxford, UK
REVIEW RETURNED	21-Dec-2016

GENERAL COMMENTS	The authors have responded appropriately to my comments.

REVIEWER	Yoko Yokoyama Keio University, Japan
REVIEW RETURNED	02-Jan-2017

GENERAL COMMENTS	The manuscript has been revised well. I have only one comment as follows. Study selection criteria: Some papers have more than one different length of outcomes (e.g. 4 weeks and 3 months intervention). Therefore, it would be better to decide which outcome will be choose previously (for example longer intervention).

REVIEWER	George A. Kelley West Virginia University, USA
REVIEW RETURNED	01-Jan-2017

GENERAL COMMENTS	GENERAL COMMENTS

The authors have been very responsive to my previous review and I appreciate their efforts. My three remaining specific comments appear below with reference to line numbers as inserted by the authors for the first two comments.

SPECIFIC COMMENTS
* Line 122 – Suggest that you insert "(direct evidence)." at the end of this sentence

* Line 209 – Place a comma after the word "example"

* In the original submission, I stated the following with respect to Page 12, lines 239 through 241 – You say that you will use ranking probabilities and surface under the cumulative ranking curves (SUCRA), which I'm fine with. However, others may argue that since treatment effects are considered as fixed parameters when a frequentist versus Bayesian approach is used, SUCRA values are no better than simply ranking treatments by their point estimates (see: Rucker, G. and G. Schwarzer (2015). "Ranking treatments in frequentist network meta-analysis works without resampling methods." BMC Medical Research Methodology 15: 58.)

Your response to my comment above was as follows: "Comment: We do not agree with the reviewer that "SUCRA values are no better than simply ranking treatments by their point estimates" and this is nowhere reported in the paper by Rucker and Schwarzer. The paper says that: "From a Bayesian perspective, parameters such as those describing the relative effectiveness of two treatments are random variables and as such have a probability distribution. Thus statements such as 'treatment A is superior to treatment B with probability 60 %' or 'Treatment A ranges under the three best of ten treatments with probability 80 %' are possible. By contrast, from a frequentist perspective, treatment effects are thought as fixed parameters and thus, strictly speaking, a concept like 'the probability that A is better than B' does not make sense." The point the authors want to make is that when the analysis is performed in a Frequentist framework is not very intuitive to use ranking probabilities. However, in fact within Stata ranking probabilities are estimated using a Bayesian approach and therefore they take into account the uncertainty of the relative effects. The authors clarify in their paper that "we propose a frequentist analogue to SUCRA which we call P-score that works without resampling" and "we demonstrate that the numerical values of SUCRA and P-Score are nearly identical". Consequently, we prefer to stick with the ranking probabilities and SUCRAs as this in the only available method in Stata to date, which is the software we will use for all analyses."

First, I appreciate the detailed response. However, if you look closely at my original comment, I clearly point out that I was fine with what you were proposing. Thus, to say you disagree with me is incorrect as I was referring to what other reviewers, particularly those with statistical expertise in network meta-analysis, might be concerned with. Bottom line – I'm fine with what you originally proposed. Regardless, I appreciate the additional information you provided in the revision. One final suggestion – In your future responses, you may want to try and avoid saying that you can't conduct a certain analysis because the software you plan to use doesn't allow for such. Software should usually not be a limiting factor when analyzing data. One can always write code to conduct

the analysis one desires.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

The manuscript has been revised well. I have only one comment as follows.

Study selection criteria: Some papers have more than one different length of outcomes (e.g. 4 weeks and 3 months intervention). Therefore, it would be better to decide which outcome will be choose previously (for example longer intervention).
Comment: has been added (lines 103-104).

Reviewer: 3

GENERAL COMMENTS
The authors have been very responsive to my previous review and I appreciate their efforts. My three remaining specific comments appear below with reference to line numbers as inserted by the authors for the first two comments.

SPECIFIC COMMENTS
* Line 122 – Suggest that you insert "(direct evidence)." at the end of this sentence
Comment: has been added

* Line 209 – Place a comma after the word "example"
Comment: has been added

* In the original submission, I stated the following with respect to Page 12, lines 239 through 241 – You say that you will use ranking probabilities and surface under the cumulative ranking curves (SUCRA), which I'm fine with. However, others may argue that since treatment effects are considered as fixed parameters when a frequentist versus Bayesian approach is used, SUCRA values are no better than simply ranking treatments by their point estimates (see: Rucker, G. and G. Schwarzer (2015). "Ranking treatments in frequentist network meta-analysis works without resampling methods." BMC Medical Research Methodology 15: 58.)

Your response to my comment above was as follows: "Comment: We do not agree with the reviewer that "SUCRA values are no better than simply ranking treatments by their point estimates" and this is nowhere reported in the paper by Rucker and Schwarzer. The paper says that: "From a Bayesian perspective, parameters such as those describing the relative effectiveness of two treatments are random variables and as such have a probability distribution. Thus statements such as 'treatment A is superior to treatment B with probability 60 %' or 'Treatment A ranges under the three best of ten treatments with probability 80 %' are possible. By contrast, from a frequentist perspective, treatment effects are thought as fixed parameters and thus, strictly speaking, a concept like 'the probability that A is better than B' does not make sense." The point the authors want to make is that when the analysis is performed in a Frequentist framework is not very intuitive to use ranking probabilities. However, in fact within Stata ranking probabilities are estimated using a Bayesian approach and therefore they take into account the uncertainty of the relative effects. The authors clarify in their paper that "we propose a frequentist analogue to SUCRA which we call P-score that works without resampling" and "we demonstrate that the numerical values of SUCRA and P-Score are nearly identical". Consequently, we prefer to stick with the ranking probabilities and SUCRAs as this in the only available method in Stata to date, which is the software we will use for all analyses."

First, I appreciate the detailed response. However, if you look closely at my original comment, I clearly point out that I was fine with what
you were proposing. Thus, to say you disagree with me is incorrect as I was referring to what other reviewers, particularly those with
statistical expertise in network meta-analysis, might be concerned with. Bottom line – I'm fine with what you originally proposed. Regardless, I appreciate the additional information you provided in the revision.

RE: In our response we meant to say that we do not agree with the statement that "SUCRA values are no better than simply ranking
treatments by their point estimates". Probably we misunderstood and we believed that the reviewer agrees with this statement, although it seems that the reviewer was only expressing concerns of other people and he agrees with our intended strategy for ranking. However, in that case it is not clear to us what was the actual aim of this comment. We thank the reviewer for raising our awareness on the concerns that some people may have on our methods but we have followed all the discussions on this topic over the last years and we selected this methodology after careful consideration.

One final suggestion – In your future responses, you may want to try and avoid saying that you can't conduct a certain analysis because the software you plan to use doesn't allow for such. Software should usually not be a limiting factor when analyzing data. One can always write code to conduct the analysis one desires.

RE: We thank the reviewer for his suggestion but in our response we did not say we cannot use the P-scores because there is no command in Stata for this. We said that since the P-scores and the SUCRAS are totally equivalent (as we explained) and SUCRAS already have been implemented in Stata, we see no point to change to P-scores. This is a clinical and not methodological paper and the aim to infer on the comparative effectiveness of different interventions. Software development is not typically a part of such papers unless it is really necessary.

VERSION 3 – REVIEW

REVIEWER	IGHO ONAKPOYA UNIVERSITY OF OXFORD, UK
REVIEW RETURNED	13-Jan-2017

GENERAL COMMENTS	THE AUTHORS HAVE ADDRESSED MY CONCERNS

REVIEWER	Yoko Yokoyama Keio University
REVIEW RETURNED	18-Jan-2017

GENERAL COMMENTS	Thank you for the revised version of the manuscript. The comments were taken into consideration appropriately.

REVIEWER	George A. Kelley West Virginia University, USA
REVIEW RETURNED	24-Jan-2017

GENERAL COMMENTS	The authors have been responsive to my previous and minor comments.

	One final note - There appears to be a misunderstanding that may have to do with language barriers. Specifically, based on your response about the use of Stata software, most people fluent in the English-language would most likely interpret your response the same way I did. Also, I think what you mean here does not have to do with software development but rather code written within an existing statistical package such as STATA. That's where I was going with that statement. Finally, as a national and international authority on applied systematic reviews with meta-analysis as well as an NIH R01 funded Principal Investigator for approximately 20 years, I agree that most people tend to use existing statistical routines to conduct their meta-analytic work. However, I have no hard data to support such.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 3

The authors have been responsive to my previous and minor comments.

One final note - There appears to be a misunderstanding that may have to do with language barriers. Specifically, based on your response about the use of Stata software, most people fluent in the English-language would most likely interpret your response the same way I did.

Also, I think what you mean here does not have to do with software development but rather code written within an existing statistical package such as STATA. That's where I was going with that statement.

Finally, as a national and international authority on applied systematic reviews with meta-analysis as well as an NIH R01 funded Principal Investigator for approximately 20 years, I agree that most people tend to use existing statistical routines to conduct their meta-analytic work. However, I have no hard data to support such.

Comment: Thank you very much for the clarification. We regret to have caused this misunderstanding.

VERSION 4 – REVIEW

REVIEWER	George A. Kelley West Virginia University, USA
REVIEW RETURNED	09-Feb-2017

GENERAL COMMENTS	The authors have adequately addressed my comments.